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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/932,183	08/17/2001	David A. Estell	GC394C1-US	5103
5100	7590	11/17/2003	EXAMINER	
GENENCOR INTERNATIONAL, INC. ATTENTION: LEGAL DEPARTMENT 925 PAGE MILL ROAD PALO ALTO, CA 94304			MOORE, WILLIAM W	
			ART UNIT	PAPER NUMBER
			1652	

DATE MAILED: 11/17/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

1cc

Office Action Summary	Application No. 09/932,183	Applicant(s) ESTELL, DAVID A.	
	Examiner William W. Moore	Art Unit 1652	

-- **Th MAILING DATE of this communication appears on the cover sheet with the correspondence address --**

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☐ Responsive to communication(s) filed on ____.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-10 is/are pending in the application.
- 4a) Of the above claim(s) 11-25 is/are withdrawn from consideration.
- 5) ☐ Claim(s) ____ is/are allowed.
- 6) ☒ Claim(s) 1-10 is/are rejected.
- 7) ☐ Claim(s) ____ is/are objected to.
- 8) ☐ Claim(s) ____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on ____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on ____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☒ Certified copies of the priority documents have been received in Application No. 09/308,375.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
 a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s). ____. |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449) Paper No(s) <u>3</u> . | 6) <input type="checkbox"/> Other: _____ |

Art Unit: 1652

DETAILED ACTION

Election/Restrictions

Restriction is required under 35 U.S.C. §§121 and 372. This application contains the following inventions or groups of inventions which are not so linked as to form a single
5 general inventive concept under PCT Rule 13.1. In accordance with 37 CFR 1.499, applicant is required, in reply to this action, to elect a single invention to which the claims must be restricted.

10 Group 1, claims 1-10, drawn to a first product, a gram-positive microorganism maintaining a mutation or deletion within a nucleic acid sequence, a gene, that encodes a metalloprotease inactivated as a result of the mutation or deletion, classified in class 435, subclass 252.3.

15 Group 2, claims 11-20, drawn to a second product, a formulated composition comprising an active metalloprotease, which composition may be cleaning composition, a composition for treating a textile, or an animal feed, classified, *inter alia*, in class 510, subclass 320.

Group 3, claims 21-24, drawn to a third product, an expression vector that comprises a nucleic acid sequence encoding an active metalloprotease, as well as a host cell transformed with the expression vector, classified, *inter alia*, in class 435, subclass 320.1.

20 Group 4, claim 25, drawn to a first method of use of a fourth product, a nucleic acid probe having a sequence complementary in whole or in part to a nucleic acid sequence encoding an active metalloprotease, in detecting and isolating a metalloprotease gene in the genome of a gram-positive microorganism, classified, in class 435, subclass 6.

25 The invention of Group 1 and the inventions listed as Groups 2-4 do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: The inventions of Groups 2-4 may not, as claimed, comprise or utilize a gram-positive microorganism of Group 1 having a mutation or deletion within a nucleic acid sequence, a
30 gene, encoding a metalloprotease inactivated as a result of the mutation or deletion, thus cannot share a same special technical feature with an invention Group 1.

The invention of Group 2 and the inventions listed as Groups 3 and 4 do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:
35 The inventions of Groups 3 and 4 may not, as claimed, comprise or utilize a composition

Art Unit: 1652

of Group 2 comprising an active metalloprotease of a gram-positive microorganism, thus cannot share a same special technical feature with an invention of Group 2.

The inventions listed as Groups 3 and 4 do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: The invention of Group 4 may not, as claimed, utilize an expression vector of Group 3 comprising a nucleic acid sequence encoding an metalloprotease, or a host cell transformed with the expression vector, thus cannot share a same special technical feature with an invention of Group 3.

During a telephone conversation with Ms. Victoria L. Boyd on February 13, 2002, a provisional election was made with traverse to prosecute the invention of Group 1, claims 1-10. Affirmation of this election must be made by applicant in replying to this Office action. Claims 11-25 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Priority

Applicant is reminded that in order for a patent issuing on the instant application to obtain the benefit of priority based on priority papers filed in parent Application No. 09/308,375 under 35 U.S.C. § 119(a)-(d) or (f), a claim for such foreign priority must be made in this application. In making such claim, applicant may simply identify the application containing the priority papers. It is noted that this application appears to claim subject matter disclosed in prior Application No. 09/308,375, filed May 14, 1999. A reference to the prior application must be inserted as the first sentence of the specification of this application or in an application data sheet (37 CFR 1.76), if applicant intends to rely on the filing date of the prior application under 35 U.S.C. §§ 119(e) or 120. See 37 CFR 1.78(a). For benefit claims under 35 U.S.C. § 120, the reference must include the relationship (i.e., continuation, divisional, or continuation-in-part) of all nonprovisional applications. Also, the current status of all nonprovisional parent applications referenced should be included.

Because this application is a utility application filed under 35 U.S.C. § 111(a) on or after November 29, 2000, the specific reference to the prior application must be

Art Unit: 1652

submitted during the pendency of the application and within the later of four months from the actual filing date of the application or sixteen months from the filing date of the prior application. This time period is not extendable and a failure to submit the reference required by 35 U.S.C. §§119(e) and/or 120, where applicable, within this time period is considered a waiver of any benefit of such prior application(s) under 35 U.S.C. §§119(e), 120, 121 and 365(c). A priority claim filed after the required time period may be accepted if it is accompanied by a grantable petition to accept an unintentionally delayed claim for priority under 35 U.S.C. §§119(e), 120, 121 and 365(c). The petition must be accompanied by (1) the reference required by 35 U.S.C. §§120 or 119(e) and 37 CFR 1.78(a)(2) or (a)(5) to the prior application (unless previously submitted), (2) a surcharge under 37 CFR 1.17(t), and (3) a statement that the entire delay between the date the claim was due under 37 CFR 1.78(a)(2) or (a)(5) and the date the claim was filed was unintentional. The Director may require additional information where there is a question whether the delay was unintentional. The petition should be addressed to: Mail Stop Petition, Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450.

Information Disclosure Statement

The information disclosure statement filed August 29, 2003, does not fully comply with the requirements of 37 CFR 1.98 because four documents cited, each of which is lined-through on the accompanying PTO Forms 1449, are entire books and no particular page(s) or chapter(s) are cited therein. A fifth citation, to an International Search Report, is lined-through because it is no more than a compilation of citation and an incomplete citation on the final sheet of the accompanying PTO Forms 1449, Lazarevic et al., has been completed by the Examiner because this publication was identified in a sequence search. Since the submission appears to be *bona fide*, Applicant may provide a further, Supplemental, Information Disclosure Statement in compliance with 37 CFR 1.98 setting forth complete citations of, as well as copies of the relevant pages or chapters cited in, any of the four documents that Applicant desires be considered.

Claim Objections

Claims 1, 4, and 5 are objected to because of the following informalities: Each of claims 1, 4 and 5 recite an acronym, "MP", which fails to adequately convey to the public reading the claims the nature of the feature of the subject matter that is intended, a metalloprotease-encoding nucleic acid in claim 1 and the encoded metalloprotease of

Art Unit: 1652

claims 4 and 5. Claim 8 lacks standard English grammar in its recitation of "protein selected from the group consisting of hormone, enzyme, growth factor and cytokine" where each member of the group to be selected is a plural genus, thus should be recited in the plural. Claim 10 lacks standard English grammar in erroneously inserting the indefinite article, "a", before the plural term "proteases". Appropriate correction is required.

Claim Rejections - 35 USC § 101

35 U.S.C. §101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 1-5 are rejected under 35 U.S.C. §101 because the claimed invention is directed to non-statutory subject matter.

Claims 1-5 describe a *Bacillus subtilis* cell that is a product of Nature because no claim states a descriptive recitation indicating that a claimed "microorganism" is a product of the activity of a person, e.g., an "isolated . . . microorganism having a mutation or deletion resulting in the inactivation of the [metalloprotease] activity".

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. §112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-3 and 5-10 are rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification fails to exemplify or describe either the preparation or the isolation of the subject matters of the multitude of "gram-positive" microorganisms of claims 1-3 and 5-10. While the specification discloses that the nucleic acid sequence of SEQ ID NO:1 is endogenous to *Bacillus subtilis*, i.e., present in its chromosome, it does not indicate

Art Unit: 1652

that this or a substantially similar nucleic acid sequence exists in other *Bacillus* species, nor in other gram-positive prokaryotes. The specification fails to exemplify, disclose, or teach a *Bacillus* species other than *B. subtilis* wherein a deletion or other mutation of all or part of the nucleic acid sequence is made. It is agreed that a structural motif set forth at page 2 of the specification and present in the active site of members of the M23 family of metalloproteases, the internal tripeptide HXH where X may be any amino acid, occurs in the encoded amino acid sequence of SEQ ID NO:2 of the specification, but this structural feature is but a tiny fraction of the overall amino acid sequence of SEQ ID NO:2 and is an insufficient basis for identifying nucleic acid sequence regions in chromosomes of “gram-positive microorganisms” generally that might establish the broad genus of microorganisms indicated in claims 1-3 and 6-10. This is because HXH tripeptides may occur in proteins other than metalloproteases, and a tripeptide sequence can in no way define the rest of the amino acid sequence of a metalloprotease.

Claim 5 is included in this rejection because page 6 of specification identifies only the *Bacillus subtilis* strain I-168 as the microorganism wherein the chromosomal nucleic acid sequence region encoding the metalloprotease having an amino acid sequence disclosed herein, that set forth in SEQ ID NO:2, commences at a nucleotide position 2248kb from a point of origin which, according to page 8 of the specification, is the point of origin of chromosomal replication. Neither can claim 5 nor the text at page 3, lines 14-18, of the specification, be considered to define a microorganism of the claims because the text describes a chromosomal “address” for a gene rather than its structure or the structure of an encoded product. The only other disclosure in the specification suggesting the structure of a claimed microorganism is based on a discussion of percentage homology of nucleic acid sequences encoding other, undisclosed, metalloproteases at page 6 of the specification where the comparison for determining homology is presumably made to the nucleic acid

Art Unit: 1652

sequence set forth in SEQ ID NO:1. Thus claims 1, 2 and 4-10 reach microorganisms having mutated or deleted genes encoding metalloproteases that that may differ, according to page 7 of the specification, at 5%, 10% or 20% of the positions in the encoded amino acid sequence of SEQ ID NO:2, yet neither the claims nor the specification describe where the differences occur, nor what the differences might be. “While one does not need to have carried out one’s invention before filing a patent application, one does need to be able to describe that invention with particularity” to satisfy the description requirement of the first paragraph of 35 U.S.C. §112. *Fiers v. Revel v. Sugano*, 25 USPQ2d 1601, 1605 (Fed. Cir. 1993). The characteristics that the specification proposes as descriptions of metalloprotease genes to be inactivated by mutation or deletion cannot be extended to describe as yet unknown, undisclosed, gram-positive microorganisms, and indeed cannot exclude prior art *Bacillus* species wherein metalloprotease genes were inactivated by others.

The Court of Appeals for the Federal Circuit held that a claimed invention must be described with such “relevant identifying characteristic[s]” that the public could know that the inventor possessed the invention at the time an application for patent was filed, rather than by a mere “result that one might achieve if one had made that invention”. *University of California v. Eli Lilly*, 119 F.3d 1559, 1568, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997). The specification does not suggest transferring an inactivated metalloprotease gene from the disclosed source, *Bacillus subtilis*, to another microorganism thus claims 1-3 and 5-10 must be construed to describe as yet unknown, undisclosed, gram-positive microorganisms which Applicant did not possess at the time the specification was filed.

Claims 1-3 and 5-10 are rejected under 35 U.S.C. §112, first paragraph, because the specification, while being enabling for *Bacillus subtilis* cells having a mutation in, including a deletion of all or part of, a nucleic acid sequence encoding a metalloprotease having the amino acid sequence set forth in SEQ ID NO:2 which inactivates or eliminates the metalloprotease, does not reasonably provide enablement for finding or making other, generic, gram-positive microorganisms having inactivating mutations of nucleic acid sequences encoding an amino acid sequence related to SEQ ID NO:2. The specification

Art Unit: 1652

does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

It is agreed that mutations comprising either a deletion of all or part of a nucleic acid sequence encoding the amino acid sequence of SEQ ID NO:2 or substitutions or insertions of or one or more codon that will disrupt, at least, the zinc metalloprotease motif indicated in the specification will inactivate a metalloprotease encoded by SEQ ID NO:1 herein, thus provide a *Bacillus subtilis* cell of claims 1-10. But claims 1-3 and 5-10 are not limited to *Bacillus subtilis* cells comprising an inactivated metalloprotease gene that had encoded an amino acid sequence set forth in SEQ ID NO:2, prior to deletion or other disruptive mutation, contemplating instead mutated gram-positive microorganisms other than *Bacillus subtilis*. Yet the specification fails to describe, teach, suggest, or otherwise support amino acid insertions, deletions, or substitutions at sites beyond positions in a zinc metalloprotease motif in native metalloproteases of gram-positive microorganisms generally, and the prior art made of record herewith cannot compensate for the deficiencies of the specification.

It is well settled that 35 U.S.C. § 112, first paragraph, requires that a disclosure be sufficiently enabling to allow one of skill in the art to practice the invention as claimed without undue experimentation and that unpredictability in an attempt to practice a claimed invention is a significant factor supporting a rejection under 35 U.S.C. § 112, first paragraph, for non-enablement. See, *In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) (recognizing and applying the "Forman" factors). Cf., *Ex parte Forman*, 230 USPQ 546, 547 (Bd. Pat. App. & Int. 1986) (citing eight factors relevant to analysis of enablement). The standard set by the CCPA, the precursor of the Court of Appeals for the Federal Circuit, is not to "make and screen" any and all possible alterations because a reasonable correlation must exist between the scope asserted in the claimed subject matter and the scope of guidance the specification provides. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 25 (CCPA 1970) (scope of enablement varies inversely with the degree of unpredictability of factors involved in physiological activity of small peptide hormone).

Art Unit: 1652

The Federal Circuit approved the standard set by the CCPA in *Genentech, Inc. v. Novo-Nordisk A/S*, 42 USPQ2d 1001 (Fed. Cir. 1997). Applying the “*Forman*” factors discussed in *Wands, supra*, to Applicant’s disclosure, it is apparent that:

- 5 a) the specification lacks guidance for inactivating a metalloprotease-encoding nucleic acid sequence in gram-positive organisms generally,
- b) the specification lacks working examples wherein any metalloprotease-encoding nucleic acid sequence is located and inactivated in a gram-positive organism other than a *Bacillus* species, and,
- 10 c) in view of the prior art publications of record herein, the state of the art and level of skill in the art do not support such alteration.

Thus the scope of claims 1-3 and 5-10 that embraces gram-positive microorganisms comprising inactivating mutations of genes encoding metalloproteases that differ in amino acid sequence from that set forth in SEQ ID NO:2 is considered to be unsupported by the specification, even if taken in combination with the teachings available in the prior art.

- 15 The following is a quotation of the second paragraph of 35 U.S.C. §112:
The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.
- 20 Claims 1-10 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Neither the independent claim 1 or its dependent claim 4 recite a sequence identifier for a nucleic acid sequence encoding a metalloprotease that can be inactivated by mutation or deletion, or the amino acid sequence of a disclosed metalloprotease that can be inactivated by mutation or deletion of the encoded amino acid sequence, e.g., the nucleic acid sequence set forth in SEQ ID NO:1 or the metalloprotease having the amino acid sequence set forth in SEQ ID NO:2. This is particularly crucial for claim 4, which refers to the specific sequence disclosed in Figures 1A-1O. Claims 2, 3, and 5-10 are subject to this rejection because they fail to otherwise clarify the ambiguity of claims 1 or 4 from which they depend. This rejection may be overcome by amending claim 1 to insert a further clause that states an absent sequence identifier, e.g., “. . . part or all of the

Art Unit: 1652

[chromosomal] nucleic acid [sequence] encoding [the] metalloprotease having the amino acid sequence set forth in SEQ ID NO:2, said mutation . . .". Claim 5 is independently indefinite in reciting, "amino acid sequence encoding by the MP nucleic acid" because amino acid sequences are not regarded in the relevant art of molecular biology of encoding nucleic acids; in addition, claim 5 is indefinite in stating "nucleic acid found about 2248kb from the point of origin" because this recitation erroneously indicates that Applicant intends a single nucleic acid, where Applicant instead discloses in the specification that it is a nucleic acid sequence commencing at the indicated position, and because it fails to indicate what is originated at any particular point in any context.

Claims 6 and 7 are independently indefinite in reciting, "comprises nucleic acid encoding", because this statement erroneously indicates that a single nucleic acid, which may be a nucleotide, can encode something. Claim 10 is indefinite in failing to clearly distinguish between genera and sub-genera in its improper recitation of a Markush group that includes the term "such as" because a broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. Note the explanation given by the Board of Patent Appeals and Interferences in *Ex parte Wu*, 10 USPQ2d 2031, 2033 (Bd. Pat. App. & Inter. 1989), as to where broad language is followed by "such as" and then narrow language. The Board stated that this can render a claim indefinite by raising a question or doubt as to whether the feature introduced by such language is (a) merely exemplary of the remainder of the claim, and therefore not required, or (b) a required feature of the claims. Note also, for example, the decisions of *Ex parte Steigewald*, 131 USPQ 74 (Bd. App. 1961); *Ex parte Hall*, 83 USPQ 38 (Bd. App. 1948); and *Ex parte Hasche*, 86 USPQ 481 (Bd. App. 1949).

Art Unit: 1652

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. §102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

Claims 1-3 and 6-10 are rejected under 35 U.S.C. §102(b) as being anticipated by Ferrari et al., U.S. Patent No. 5,264,366, made of record with Applicant's Information Disclosure Statement filed 29 August 2003, or either of Sloma et al., U.S. Patents Nos. 5,589,383 and 5,620,880, both made of record herewith.

Each of Ferrari et al., Sloma et al.('383), and Sloma et al.('880) disclose preparation of *Bacillus subtilis* host cells that comprise an inactivating mutation – in each disclosure this is a deletion of a region of the cell's chromosome comprising a nucleic acid sequence encoding a metalloprotease – that results in inactivating the cell's secreted metalloprotease activity. See, e.g., Figures 9-14 of Ferrari et al., and Figures 1 and 2 of each of Sloma et al. Each of Ferrari et al., Sloma et al.('383), and Sloma et al.('880), disclose, see, e.g., col. 8, line 39, through col. 9, line 3, and Examples 11 and 16 of Ferrari et al., and col. 3, lines 11-25, and col. 5, line 31, through col. 6, line 61, of Sloma et al.('383) and Sloma et al.('880), that they prepared *Bacillus subtilis* host cells comprising inactivating mutations of chromosomal regions encoding metalloprotease genes for the purpose of recombinant production of desired polypeptides, both isologous and heterologous to bacilli, including, *inter alia*, amylases, altered subtilisins, fungal proteases, peptide hormones, and vaccine components, meeting limitations of claims 1-3 and 6-10 herein.

Claims 1-3 and 7 are rejected under 35 U.S.C. §102(b) as being anticipated by Donovan et al., U.S. Patent No. 5,759,538, made of record herewith.

Donovan et al. disclose, see Figures 2 and 7-11 and Examples 10-12 the preparation of *Bacillus thuringiensis* host cells having an inactivating mutation, a deletion of a region of

Art Unit: 1652

the cell's chromosome comprising a nucleic acid sequence encoding a metalloprotease, of a metalloprotease gene that results in inactivating the cell's secreted metalloprotease activity for the recombinant production of an isologous polypeptide, an insecticidal protein, meeting limitations of claims 1-3 and 7 herein.

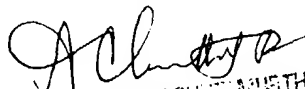
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Conclusion

While claims 4 and 5 are subject to the rejections above under 35 U.S.C. §§101 and 112, second paragraph, they are free of the prior art of record herein because neither of Kunst et al. nor Lazarevic et al., while they disclose the nucleic acid sequence of SEQ ID NO:1 herein thus inherently disclose the encoded amino acid sequence of SEQ ID NO:2
10 herein, suggest that the amino acid sequence encoded by the *Bacillus subtilis* nucleic acid sequence they disclose is a secreted metalloprotease, indeed Lazarevic et al. characterize the encoded product as a transglycosylase. Thus disclosures of Kunst et al. and Lazarevic et al. would have failed to provide any motivation to one of ordinary skill in the art at the time the invention was made to make any inactivating mutation, including a deletion, of a
15 chromosomal region comprising their commonly disclosed nucleic acid sequence to prepare a host cell claimed herein.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to William W. Moore whose telephone number is 703.308.0583. The examiner can normally be reached between 9:00AM-5:30PM EST.
20 If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy can be reached at 703.308.3804. Further fax phone numbers for the organization where this application or proceeding is assigned are 703.308.4242 for regular communications and 703.308.0294 for After Final communications. The examiner's direct FAX telephone number is 703.746.3169. Any
25 inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703.308.0196.

30 William W. Moore
October 16, 2003


PONNATHAPURA ACHUTAMURTHY
SUPERVISORY PATENT EXAMINER
TECHNOLOGICAL CENTER